UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,687	09/28/2000	David Wallach	WALLACH=25	7238

1444 7590 09/22/2006

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
SCHLAPKOHL, WALTER	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,687	WALLACH ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	mdf

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,20-24,38-40 and 42-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,20-24,38-43,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 7/11/2006 in which claims 2 and 38 were amended. Claims 2-3, 20-24, 38-40 and 42-48 are pending and under examination in the instant Office action.

Claim Objections

Claims 42 and 43 are objected to because of the following informalities: claims 42 and 43 are essentially duplicates of claims 39 and 40, respectively. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 20-24, 38-43 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to isolated proteins capable of binding to tumor necrosis factor receptor-associated 2 protein (TRAF-2) or to a component of the NF-κB complex, wherein said proteins are at least 90% identical to SEQ ID NO: 3. The claims are further drawn to proteins capable of binding to TRAF-2 and which have no more than 10 (claim 47) and no more than 5 (claim 48) amino acid changes from the amino acid sequence of SEQ ID NO: 3. The claims are further drawn to molecules having the binding portion of an antibody capable of binding to such isolated proteins. The claims encompass any protein, wherein at least a portion of the protein has 90% identity to SEQ ID NO: 3. The claims do not provide any structural information with regard to sequences with 90% identity to SEQ ID NO: 3 capable of binding to TRAF-2 or to components of the NF-κB complex selected from IKAP, IKK-alpha, IKK-beta, IKK-gamma and NIK. Thus, the rejected claims comprise a set of nucleic acid sequences that are defined by the function of the encoded protein.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a

complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes a NAP protein of SEQ ID NO: 3 that was identified in a yeast two-hybrid assay and is capable of binding NEMO and TRAF-2 (see, e.g, page 99, Table 2). No description is provided of a single variant (truncated, fused to another protein or protein domain, insertionally mutated, mutated by deletion, mutated by amino acid substitution or otherwise) that is 90% identical to SEQ ID NO: 3. No description is provided of a variant of SEQ ID NO: 3 of any kind that is capable of binding to TRAF-2 or to an NF-κB complex. Applicant claims the proteins and antibodies capable of binding to such proteins by function only (i.e., their ability to bind to TRAF-2 and the NF-κB regulatory complex), without any disclosed or known correlation between the elements and their function. The claims read on any protein that can bind to TRAF-2 as long as the protein is 90% identical to SEQ ID NO: 3, but the specification only describes one specific embodiment, NAP as represented by SEQ ID NO: 3. Furthermore, the specification does not provide a structural analysis of NAP to identify the relevant structural features that are required for binding activity. For example, is there a specific domain that can be found in multiple proteins that

would allow the skilled artisan to envision the proteins that are claimed? Are there multiple proteins that are structurally divergent that can bind to TRAF-2 or to the NF-κB complex protein recited? The skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification because the specification only discloses a single protein, rather than a representative number of species within the genus as claimed, and the specification does not indicate the relevant structural features that are required for the interaction to take place.

Even if one accepts that the example described in the specification meets the claim limitations of the rejected claims with regard to structure and function, the example is only representative of one amino acid sequence capable of binding TRAF-2. The results are not predictive of any other sequence having 90% identity with SEQ ID NO: 3 and capable of binding to TRAF-2 or to an NF-κB regulatory complex. Thus, it is impossible to extrapolate from the example described herein those amino acid molecules that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of genes or proteins that bind to TRAF-2 or NF-κB complexes and

that have 90% identity to SEQ ID NO: 3. There is no description of the relevant structural features that are required for an interaction between TRAF-2 and NAP. There is no identification of a domain that has the capacity to bind to TRAF2. Thus, the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that Applicant was in possession of the claimed genus.

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the amino acid sequences capable of fulfilling the claim limitations of claims 2, 20-24, 38-43 and 47-48, the skilled artisan would not have been able to describe the broadly claimed genus of NAP sequences that bind to TRAF-2 and to the recited components of the NF-κB complex listed in claim 38. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those amino acid sequences, aside from SEQ ID NO: 3, that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 2, 20-24, 38-43 and 47-48.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 20-24 and 38-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated protein capable of binding to TRAF-2 and having the amino acid sequence of SEQ ID NO: 3 and molecules which bind to this sequence, does not reasonably provide enablement for variants having 90% or 95% identity to SEQ ID NO: 3 having 90% identity to SEQ ID NO: 3 and having the ability to bind to TRAF-2, or variants of SEQ ID NO: 3 that have the ability to bind to NF-κB complex components selected from the group consisting of IKAP, IKK-alpha, IKK-beta, IKK-gamma and NIK. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8

USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is an isolated protein having the amino acid sequence of SEQ ID NO: 3, and variants comprising protein sequences having 90% or 95% identity to SEQ ID NO: 3, wherein each sequence has the ability to bind to the tumor necrosis factor receptor-associated 2 protein (TRAF-2) or an NF-κB complex component. The invention is also directed to molecules that have the binding portion of an antibody having the capacity to bind to the isolated proteins/variants. Thus in order to make and use the invention, the skilled artisan would be required to make a protein having the ability to bind to TRAF-2 or to IKAP, IKK-alpha, IKK-beta, IKK-gamma and NIK.

Notably, SEQ ID NO: 3 is 949 amino acids in length. Thus a protein having 90% or 95% identity to SEQ ID NO: 3 would have up to 94 and 48 amino acids changed, respectively. For example, a protein can have 90% homology to SEQ ID NO: 3, where the N-terminal 94 residues are completely different from those of SEQ

ID NO: 3; significantly, this 94 residue amino acid sequence can represent an independently functioning domain, or in some cases a functional protein of its own. Even within the context of being covalently linked to the portion of SEQ ID NO: 3 with which it has 90% identity, this 94 amino acid sequence could fold into an independently functional domain (i.e., functions with an activity that is not affected by the remaining protein having identity with SEQ ID NO: 3). Thus, the nature of the invention comprises all sequences which comprise a sequence that is 90% identical to SEQ ID NO: 3, including sequences having domains with 0% identity to SEQ ID NO: 3 or fusion proteins with 0% identity to SEQ ID NO: 3, but which still retain their ability to binding TRAF-2 or an NF-κB complex component. In the most narrow embodiment of a claimed variant of SEQ ID NO: 3, a protein can have only 1 amino acid difference from SEQ ID NO: 3 and this protein may have a conservative substitution (e.g., a substitution from among those options provided in Table 1B on page 47 of the specification).

Finally, it is important to recognize that meeting the enablement standard requires that the skilled artisan be able to make the invention, and that making the invention and identifying the invention are not synonymous.

Scope of the invention. The scope of the invention is very broad. As indicated in the Nature of the Invention, when interpreted as broadly as possible and in view of the mathematical limitations, Applicant has claimed any protein comprising an amino acid sequence that is 90% identical to SEQ ID NO: 3 that has the capacity to bind to TRAF-2 or an NF-κB complex component. Even in the context of a protein having 95% identity to SEQ ID NO: 3, and wherein the protein is of the same length as SEQ ID NO: 3, the claims include a protein that can have an independently functioning domain within the context of a larger protein (essentially a gene fusion), wherein the product of the gene fusion has the ability to bind to TRAF-2 or an NF-κB complex component. Additionally, the claims include antibodies that recognize fragments of variants having 90% or 95% identity to SEQ ID NO: 3, such as the 94 amino acid sequences which may have no identity with SEQ ID NO: 3.

State of the art and Level of skill in the art. The State of the Art concerning SEQ ID NO: 3 is silent. There is no indication in the prior art of the particular sequence, thus it is a novel sequence. However, there is also no indication in the prior art that guides the skilled artisan to be able to make a protein having 90% or 95% identity to SEQ ID NO: 3, or even a variant thereof with one conservative amino acid substitution,

wherein the variant retains the ability to bind TRAF-2 or NF-κB complex components. This is because there is no disclosure in the prior art indicating the minimum sequence/structural requirements for SEQ ID NO: 3 to bind to TRAF-2 or an NF-κB complex components. In the absence of such teachings, the skilled artisan could not make and use the claimed fragments and variants that retain the activity.

The instant application is claiming protein variants that have the functional ability to bind to TRAF-2 based on homology alone. As it regards the general art of predicting function based on homology, the prior art indicates the unpredictability associated with such an endeavor. A particular example involves the identification of a specific protein involved in Pendred Syndrome, PDS. PDS was originally identified by Everett *et al.* (*Nature Genetics* **17**: 411-422, 1997; cited previously; see entire document; henceforth Everett), who predicted that the PDS gene product encoded a sulphate ion transport protein based simply on its homology to a family of known sulphate ion transporters (see for example the Abstract and page 419, right column, second full paragraph). However, a subsequent study performed by Scott *et al.* (*Nature Genetics* **21**: 440-443, 1999; cited previously; see entire document; henceforth Scott) indicated that PDS was in fact not a sulphate ion transporter. In fact, PDS was

completely unable to transport sulphate ions across a membrane (see for example the Abstract and page 440, the paragraph bridging the left and right columns). Rather, Scott discovered that PDS was a chloride and iodide ion transporter (see for example page 440, right column, second and third full paragraphs), a finding that Scott indicates as underscoring the importance of confirming the functions of proteins, even in the face of significant homology (see for example page 441, left column, third full paragraph). This is further supported in the article by Berendsen (*Science* **282**:642-643, 1998; cited previously), which approaches the problem of predicting structure-function relationships based on homology from the perspective of high-performance computing. Berendsen indicates that, while it is desirable to be able to predict structure from function, it is extremely elusive, and is similar to King Arthur's quest for the Holy Grail (see for example page 643, paragraph bridging the left and central columns). Thus, the state of the art clearly indicates that assigning a function to a protein based on homology alone is highly unpredictable.

Number of working examples and Guidance provided by Applicant. The instant specification provides the identification of a protein indicated as SEQ ID NO: 3, and describes its ability to bind to TRAF-2 and NEMO. However, the characterization of the

protein ends there, with no indication of what sequences or domains of SEQ ID NO: 3 are required for this interaction with SEQ ID NO: 3. Armed with only this teaching, the skilled artisan would not be able to make the claimed invention of variants of SEQ ID NO: 3 that can bind to TRAF-2 or to an NF-κB complex component.

The instant specification provides teachings that are known in the art that can be used to identify protein sequences that bind to other protein sequences; such teachings include two-hybrid protein interaction systems and co-immunoprecipitation assays. The specification indicates that these teachings can be used to identify fragments, variants, and fragments of variants of SEQ ID NO: 3 that have the ability to bind to TRAF-2, and suggests that such experimentation would not be undue. However, as indicated in the Nature of the Invention section of the Wands analysis, the ability to identify is not commensurate with the ability to make and use, which is the standard for meeting the enablement requirement.

Unpredictability of the art and Amount of experimentation required. The invention is highly unpredictable, and requires a good deal of trial and error experimentation in order to make and use the claimed invention. There is nothing in either the prior art or the instant specification to indicate what variants

of SEQ ID NO: 3 are capable of binding to TRAF-2 because there is no indication of what sequence or structural requirements of SEQ ID NO: 3 are required for this binding activity. Therefore, without the knowledge of the TRAF-2 binding domain(s) of SEQ ID NO: 3, the skilled artisan could not predictably make variants of SEQ ID NO: 3 that bound to TRAF-2 or NF-κB complex components because the skilled artisan could not predictably make a mutation that does not affect the binding activity of SEQ ID NO: 3. Furthermore, the skilled artisan could not predictably make any protein comprising an amino acid sequence having 90% identity to SEQ ID NO: 3 fused to any other protein domain such that it binds to TRAF-2 or NF-κB complex components.

The teachings that there are assays to identify what variants of SEQ ID NO: 3 will bind to TRAF-2 does not assist in the ability to *make and use* these variants; it is reiterated that the ability to identify does not translate into the ability to make and use. Rather, the fact that an assay is required to identify these proteins represents an indication that unpredictable and undue trial and error experimentation is required to make and use the claimed invention. Rather, the requirement for an assay to identify variants of SEQ ID NO: 3 that have the ability to bind to TRAF-2 represents an invitation to experimentation in the absence of any significant guidance in

either the prior art or the instant specification concerning the sequence/structural requirements for SEQ ID NO: 3 to bind to TRAF-2 and/or to NF-κB complex components.

In conclusion, it is urged that the ability to identify a sequence with a function does not equate to the ability to make and use such a sequence, which is the standard for meeting the enablement requirement of 35 USC § 112, first paragraph. The instant claims are very broad, not only including variants with a small number of conserved amino acid changes in domains outside of the proteins functional domains, but including an amino acid sequence *comprising* an amino acid sequence that is 90% identical to SEQ ID NO: 3 that has a particular activity. Neither the instant specification nor the prior art provides any guidance indicating the sequence and structural requirements for SEQ ID NO: 3 to bind to TRAF-2. Significantly, the variants of SEQ ID NO: 3 having the ability to bind to TRAF-2 are claimed based simply on homology to the SEQ ID NO: 3, with the prediction of a functional capacity to bind to TRAF-2 based simply on that homology; however, the prior art indicates that predicting function based simply on sequence homology is unpredictable. Thus, in order to make the claimed invention (as opposed to identifying the claimed invention) in the absence of adequate teachings by either the prior art or the instant

specification, the skilled artisan would be required to practice undue and trial and error experimentation to test all of the claimed variants for function. Therefore, it is determined that the broad scope of the invention is not fully enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The rejection of claims 2, 38-40, 42-43 and 47 under 35 U.S.C. 102 (a) as being anticipated by Stratton (see Genbank submission of November 29, 1999; cited previously) is hereby WITHDRAWN because the priority date for the Stratton reference has been verified as later than the effective filing date of Applicant's invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 21-24 and 44-46 under 35 U.S.C. 103(a) as being unpatentable over Stratton (see citation above) in view of Applicant's admission in the paper filed 9/23/2002 that it would be obvious for one of skill in the art to make antibodies to a protein that is known in the prior art is hereby WITHDRAWN because the priority date for the Stratton reference has been verified as later than the effective filing date of Applicant's invention.

Allowable Subject Matter

Claims 3 and 44-46 are objected to as being dependent upon a rejected base claim but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the

Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

September 15, 2006

NANCY VOGEL
PRIMARY EXAMINER